spent in the interview, and requested to enter the amended claims set forth in the claim listing, and reconsider the rejections in view of the following remarks.

REMARKS

The Examiner maintained the rejection of claims 76-83 and 86-92 under Section 102(e) over Gombinski (US 6,297,062), which relates to:

> a method for separating at least one species of biological entities from a sample solution, by contacting the sample with a matrix of magnetic particles formed on a substrate such as a sheet a gel, etc. The particles in the matrix are coupled to entities capable of specifically binding to the species of biological entities to be separated. [*see* Abstract]

Further, as set forth in the Summary of the Invention (col. 5, lines 38-53) of Gombinski:

> Preferably, the matrix should contain magnetic particles, coupled to several different species of second members of the pair forming groups, for example, to different types of antibodies, wherein all the magnetic particles which are coupled to a specific species of said second member are present in a discrete location in the matrix, which is different than the location of the other magnetic particles. When the sample is contacted with said matrix, and each species of biological entities, (first member of the pair forming group, for example, a specific antigen) binds to its specific second member of the pair forming group (for example its specific antibody) ***which is present in a discrete location in the matrix. Thus each species of the biological entities is spatially separated, in a discrete location, from the other entities,*** and due to the magnetic properties of the magnetic particles, each species may be obtained separately. [emphasis added]

The Examiner alleges that:

> The particle-attached ligands encoded with a chemical or physical characteristic are equivalent to the magnetic particle-attached biological entities-label. Such magnetic particles-attached biological label is attached to the substrate/matrix. The biological entities are proteins such as monoclonal antibodies or oligonucleotides such as RNA or DNA ..." *See* Office Action page 4.

It is clear, however, that the claimed "array of several different particle-attached ligands, wherein *different ligands are attached to different particles* and said particles are encoded with a chemical or physical characteristic *that permits identification of the ligand or ligands attached thereto and permits distinguishing of particles having different ligands*

attached thereto from each other" (claim 76; emphasis added) are not "equivalent" to the magnetic particles of Gombinski, with the attached "biological-entities" labels. Gombinski relates to purification by "separating at least one species of biological entities from a sample solution..." (as noted in the Abstract above), there is no need for encoded particles, and no "teaching" of them, as is clarified by the following passage from Example I (col. 16, lines 34-54):

> 200 µl from 1 µm diameter superparamagnetic *ferrous oxide particles which were coated with a functional affinity group* (Advanced Magnetics, Inc., USA) were drawn from a 50 mg/ml stock solution and were injected to 3 ml of a 2% aqueous solution of low melting point agarose (A-9414, Sigma Chemical Co., USA) at a temperature of 45° C and mixed for 1 minute by a vortex. The agarose was poured into the casting space and then covered with a 7×7 cm hot glass plate. After a few minutes at 35° C. the gel was allowed to cool and was left at room temperature for at least one hour. During this time the magnetic particles were drawn to the stripped magnet and a stripped matrix of magnetic particles at the bottom layer of the gel was then obtained. The same procedure was repeated with the uniform magnet, whereby a uniformed [sic] matrix of magnetic particles was obtained. [emphasis added]

Accordingly, the Gombinski particles are all coated with the same functional group in order to separate a specific constituent from a sample solution with which the matrix is contacted. If the constituent within the sample binds to the functional group on the particle, the binding event can be detected using a "biological entities-label." But the particles are not encoded with a "physical or chemical characteristic" or otherwise. In contrast to the invention, the particles within a uniform matrix or within a discrete location of the substrate all carry the same functional group – the "biological-entities label" merely indicates a binding event. In fact, in the preferred arrangement of the Gombinski matrix comprising magnetic particles coupled to different species, these particles - precisely because they are not encoded by a physical or chemical characteristic - must be spatially separated, in different discrete locations on the substrate.

The biological entities label, indicating the binding event, will be the same for all particles.

The Examiner states on page 4 of the Office Action that the "labels are radioactive labels, fluorescent or chemiluminscent which is a chemical tag and capable of interrogated optically." The Examiner also states at 8 that "Gombinski teaches that the location of a specific species in the matrix can be known by staining the magnetic particle matrix by means well known in the art, such as by enzymatic reaction, immunoreactions, use of fluorescent or radioactive labels and the like [citing col. 8, lines 15-22]." However, at col. 8, lines 15 to 22 it actually states:

> Once the sample is contacted with the magnetic particles' matrix, the biological entities become immobilized on the matrix ***in a discrete location of the matrix where those magnetic particles which are coupled to the appropriate second member were immobilized.*** The particles from a specific discrete location in the matrix may then be easily separated from the rest of the matrix and obtained separately. ***Thus, if the location of a specific species of biological entities in the matrix is known***, (e.g. after appropriately staining the magnetic particles' matrix by means well known in the art, such as by enzymatic reactions, immuno-reactions, use of fluorescent or radioactive labels and the like), the magnetic particles having the specific separated species attached thereto can then be easily collected from the matrix, e.g. by using a device having a tapered tip which may be magnetic or non magnetic. [emphasis added]

Again, this portion of the disclosure in Gombinski does not disclose encoding particles with a "physical or chemical characteristic," or otherwise. It is clear from the emphasized language above that the encoding of the particles in Gombinski is based on their location in the array. The "staining of the magnetic particles' matrix by means well known in the art, such as by enzymatic reactions, immuno-reactions, use of fluorescent or radioactive labels and the like," identifies a number of "biological entities" attached to particles (like a secondary goat anti-mouse antibody label will identify all mouse antibodies on particles) – but does **not** permit: "identification of the ligand or ligands attached thereto and ... distinguishing of particles having different ligands attached thereto from each other..."

The Examiner has also referred to col. 12, lines 49-50 of Gombinski, regarding probing of particles with markers. Again, this portion of Gombinski does not disclose encoded particles, but rather encoding by location. Starting from line 5 of col. 12:

> The magnetic particles may have a uniform distribution pattern in the matrix made from dots or may be non-uniformly distributed in a pattern of strips of particles and the like. ... Typically, each strip is made of dots of magnetic particles having affinity to a specific species of entities.
>
> It is possible also to have several strips of varying specificities arranged in an alternating pattern along the substrate which may be a membrane, a gel or a rigid substance.
>
> An example of a matrix of magnetic beads is shown in FIG. 1, wherein 1 is a horizontal strip of dots of magnetic particles coupled to a second member of a pair forming group having an affinity to a first species of biological entities; 2 is a strip of two lines of dots of magnetic particles coupled to second members having an affinity to a second species of biological entities; 3 is a continuous line composed of magnetic particles coupled to second members having an affinity to a third species of biological entities; and 4 and 5 are diagonal and vertical dots coupled to second members having a affinity to fourth and fifth species of biological entities, respectively ....
>
> Biological entities which were separated from the sample solution and which are bound to the magnetic particles can be subjected to various analytical probings such as: binding to monoclonal antibodies linked to detectable markers; reactions with various enzymes; contact with labeled complementary DNA fragments; staining with specific dyes such as ethidium bromide and the like, as the case may be.

The Examiner also quotes Gombinski as stating: "It was possible to use different (functional) affinity particles at predetermined locations." This further clarifies that the encoding of particles in Gombinski is by location.

The Examiner has rejected claim 85 under Section 103(a) over Gombinski in view of Nacamulli et al., which relates to determining the "rate of a biomolecular reaction, such as an enzymatic reaction or an affinity binding reaction ... using electrochemiluminescence ..." *See* Abstract. Again, Nacamulli et al. do not disclose the

claimed encoded beads, or suggest such beads, because the reaction rate is determined by monitoring luminescence intensity in one type of reaction, between one type of reactant and one type of reaction partner, and that reaction produces the change in luminescence intensity of the group of reaction partners; *See, e.g.*, Abstract:

> The reaction is conducted in an electrochemical cell with a mixture of reagents including a luminophore which will relate the concentration of a reactant, a reaction partner or the reaction product of a reaction partner to the ECL intensity. The reaction partner is a reagent which reacts with the reactant and which participates with the luminophore (or its reaction product participates with the luminophore) to cause the emission of ECL.

Accordingly, there is no reason provided by Nacamulli et al., with or without Gombinski, to make particles as set forth in independent claim 76 and thus, no motivation or suggestion to do so, and the rejection should be withdrawn.

The Examiner rejected claim 82 (should be claim 84) over Gombinski in view of Hugl et al., which relates to:

> a sensor with a novel construction for a detection method of molecules labelled with fluorescent dye for detecting these dissolved substances or analytes by energy transfer with a simple fluorescence technique and increased sensitivity in the detection as well as versatile use for different tasks and the possibility of reproducible preparation of films bound to solid surfaces. [*see* Summary of the Invention]

As set forth in the Hugl et al. Summary of the Invention (col. 2, line 59 to col. 3, line 10), the optical biosensor is for monitoring of a single type of reaction based on fluorescence energy transfer:

> a) a solid support,
>
> b) a single-layer or multilayer Langmuir-Blodgett (LB) film attached to a),

c) at least one fluorescent dye F_1 which is located in at least one of the top 4 layers of the LB film,

d) a receptor molecule which is capable of specific interaction and which is bound or located in or on the topmost layer of the LB film, and

e) a mobile fluorescent dye F_2 whose excitation band overlaps, sufficiently for an energy transfer, with the emission band of F_1 and which

e1) is covalently bonded to a ligand which is able to bind to the receptor, or which

e2) is covalently bonded to another receptor which is able to bind to the complex composed of the first receptor and ligand ...

Accordingly, there is no reason provided by Hugl et al., with or without Gombinski, to make encoded particles as set forth in independent claim 76 and thus, no motivation or suggestion to do so, and the rejection should be withdrawn.

In conclusion, all claims are in condition for allowance and such action is respectfully requested.

Respectfully Submitted,

By: _____

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